

**MORRISON & FOERSTER LLP**

Attorneys at Law  
3811 Valley Centre Drive, Suite 500  
San Diego, California 92130-2332  
Telephone: (858) 720-5100  
Facsimile: (858) 720-5125

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**OFFICIAL****To: U.S. Patent and Trademark Office****Facsimile: 703 872-9306****From: Gregory P. Einhorn, Esq.****Date: June 1, 2004**

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**Comments: Follow up submission of Signed Declaration and CV for Request for Continued Examination mailed to the USPTO on May 20, 2004.**

Attorney Docket: 22000-2066200  
Group Art Unit: 1645  
Examiner: P. A. Duffy  
Serial No.: 09/830,779  
Filing Date: November 30, 2001  
Inventor(s): Kenneth Chien, et al.

Title: A METHOD OF INHIBITION OF PHOSPHOLAMBAN ACTIVITY FOR THE TREATMENT OF CARDIAC DISEASE AND HEART FAILURE

Papers attached:

1. Declaration Under 37 C.F.R. Section 1.132 with CV (11 pages)

SD-202142



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UCSD TTIPS → 87205125  
RMB 534 RMB1

NO.661 0002

Sent By: Chien Office ;

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May-17-04 14:41;

Page 1

Attorney's Docket No.: 22000-20662.00/ SD 99-023

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Kenneth Chien, et al.

Art Unit : 1645

Serial No. : 09/830,779

Examiner : Patricia Ann Duffy

Filed : November 30, 2001

Title : A METHOD OF INHIBITION OF PHOSPHOLAMBAN ACTIVITY FOR THE  
TREATMENT OF CARDIAC DISEASE AND HEART FAILURECommissioner for Patents  
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DECLARATION UNDER 37 C.F.R. § 1.132

Sir:

OFFICIAL

1. I, Kenneth Chien, am an expert in the field of molecular biology and cardiac disease and was an expert at the time of the invention. I am a co-inventor of the above-referenced patent application and I am presently employed as a professor at the University of California, San Diego, CA, assignee of the above-referenced patent application. My resume is attached as documentation of my credentials.

2. The specification presents data that demonstrates that PLB inhibitor molecule linked (using, for example, polylysine) to a transport peptide (e.g., an antennapedia transport peptide) can induce enhanced contractility in a cardiac cell. For example, Example 4, pages 28 to 29, provides data that demonstrates that a mutant PLB molecule linked to a transport molecule via polylysine was efficiently translocated into isolated rat cardiomyocytes. These cardiomyocytes showed enhanced contractility. The results of these experiments are illustrated in Figures 5a and 5b.

3. Example 5, including Table 3, pages 29 to 31, of the above-referenced patent application describes experiments that administer a mutant PLB linked to a transport peptide to mouse cardiomyocytes. Table 3 summarizes data from those experiments. As noted on page 31, lines 9 to 11, of Example 5, while there appeared to be a trend towards a larger, faster contraction in the myocyte, T-test analysis did not identify any statistical difference due to the high variability of the data. However, while the results of Example 5's experiments were



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Page 2/3

Applicant : Kenneth Chien, et al.  
Serial No. : 09/830,779  
Filed : November 30, 2001  
Page : 2 of 2

Attorney's Docket No.: 22000-20662.00/ SD 99-025

inconclusive, the totality of the experimental evidence described in this specification overwhelming and conclusively demonstrate that exogenous mutant PLB can inhibit the activity endogenous PBL to improve cardiac contractility. Furthermore, knowledge accrued since the filing of the specification confirms that exogenous mutant PLB can inhibit the activity endogenous PBL to improve cardiac contractility.

4. The level of skill in this art at the time of the invention was very high. Screening procedures used to identify protocols to effectively apply and administer exogenous PLB protein were all well known in the art and at the time this application was filed. Using the teaching of the specification, one skilled in the art could have selected routine screening protocols known in the art at the time of the invention to determine means to effectively apply and administer exogenous PLB protein. Using the teaching of the specification, one of skill in the art could have determined appropriate protocols to apply and administer an exogenous PLB linked to a transport protein to successfully practice the claimed methods of the invention.

5. An exemplary dominant negative PLB is described, inter alia, in Example 4, page 28, lines 24 to 26, as a cargo peptide derived from the first 16 residues of PLB, or, SEQ ID NO:8. This cargo sequence could also have been derived from any segment of wild-type PLB or mutant PLB. Determining additional dominant negative PLB species could have been determined by the skilled artisan using routine screening methods, including the exemplary methods described in the specification.

6. The term "dominant negative" was well known in the art at the time of the invention and the specification uses the term as it would have been understood to one skilled in the art at the time of the invention. For example, an example of a textbook definition for "dominant negative protein" now, and at the time of the invention (the definition has not changed) is "a mutant protein that as a result of the mutation has lost activity or function and interferes with the function of its corresponding wild-type protein." Thus, at the time of the invention, and now, the skilled artisan understand that a "dominant negative protein" is a mutant



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Page 3/3

Applicant : Kenneth Chien, et al.  
Serial No. : 09/830,779  
Filed : November 30, 2001  
Page : 3 of 3

Attorney's Docket No.: 22000-20662.00/ SD 99-025

protein that as a result of the mutation has lost activity or function and the mutant protein interferes with the function of its corresponding wild-type protein.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted

Date: \_\_\_\_\_

5/14/04



Kenneth Chien



**CURRICULUM VITAE****Kenneth Randall Chien, M.D., Ph.D.**

**DATE OF BIRTH:** November 24, 1951

**HOME ADDRESS:** 7460 Pepita Way  
La Jolla, Ca 92037  
Phone: (858) 456-6281

**PROFESSIONAL ADDRESS:** UCSD Institute of Molecular Medicine, 0641  
University of California, San Diego  
La Jolla, CA 92093  
Phone: (858) 534-6835  
FAX: (858) 534-8081  
Email: kchien@ucsd.edu

**MARITAL STATUS:** Married (Patricia Ann)

**DEPENDENTS:** Daughters (Marisa Court, Elena Brooke)

**ACADEMIC BACKGROUND:**

1973 Harvard College, B.A., Cum Laude in Biology

1980 Temple University School of Medicine, M.D., Ph.D.

1980-82 Straight Medicine Internship and Residency, Parkland Memorial Hospital, Dallas, TX

1981-82 Residency in Internal Medicine, Parkland Memorial Hospital, Dallas, TX

1982-84 Clinical and Research Cardiology Fellowship, University of Texas Southwestern Medical Center, Dallas, TX

1984-87 Attending Physician, Cardiology Consult Service and Coronary Care Unit, Parkland Memorial Hospital, Dallas, TX

1984-88 Assistant Professor of Medicine, Cardiology Division, University of Texas Southwestern Medical Center, Dallas, TX

1988-92 Associate Professor of Medicine, Department of Medicine and Member, Center for Molecular Genetics, University of California, San Diego, La Jolla, CA

1992- Professor of Medicine, Department of Medicine and Member, Center for Molecular Genetics, University of California, San Diego, La Jolla, CA

1996-2000 Co-Director, UCSD Cardiovascular Center



- 1998- Director, UCSD/Salk Program in Molecular Medicine
- 2000- American Heart Association Endowed Chair in Cardiovascular Research (California Affiliate)
- 2000- Professor, The Salk Institute (Adjunct)
- 2000- Director, UCSD Institute of Molecular Medicine

**HONORS AND AWARDS: (Selected)**

- 1988-93 Established Investigator Award of the American Heart Association
- 1990- Member, American Society of Clinical Investigation
- 1991-2001 Editor-in-Chief, *Trends in Cardiovascular Medicine*
- 1991-96 Director, UCSD American Heart Association, Bugher Foundation Center for Molecular Biology
- 1991- Director, NHLBI Program Project Grant on Signaling Mechanisms for Cardiac Growth and Hypertrophy
- 1992-97 Member, Board of Scientific Counselors, National Heart, Lung and Blood Institute, Bethesda, MD
- 1993- Director, NHLBI UCSD-Salk Training Program in Cardiovascular Molecular and Cellular Biology
- 1995- Director, NHLBI SCOR Program on the Molecular Physiology of the Failing Heart
- 1995 Walter B. Cannon Memorial Award and Lectureship, American Physiological Society
- 1995 Kaiser Foundation Award and Lectureship
- 1995 NHLBI Distinguished Service Citation
- 1996 The Pasarow Foundation Medical Research Award  
(Co-recipients: Stanley B. Prusiner (Neuroscience) and Alfred G. Knudson (Cancer))
- 1996 American Heart Association - United Way Combined Health Agency Health Hero Award
- 1998 Robert M. Berne Award and Distinguished Lectureship, American Physiological Society
- 1998 Robert M. Berne Visiting Professorship, University of Virginia, Charlottesville, VA
- 1998- Member, The Pasarow Medical Research Foundation Board and Award Committee
- 1999 Calabresi Visiting Professor and Lectureship, Yale University School of Medicine, New Haven, CT
- 1999 Bloomfield-Arnold Visiting Professor and Lectureship, Case Western Reserve School of Medicine, Cleveland, OH



- 1999 Dean's Distinguished Lectureship, University of Medicine and Dentistry in New Jersey, New Brunswick, NJ
- 1999 Dean's Lecture and Stuenkel Visiting Professorship, Cornell/Rockefeller/Sloan Kettering M.D.-Ph.D. Program, New York, NY
- 2000 The 2000 Sankyo Lectureship, Kyoto University, Kyoto, Japan
- 2000 The Temple University Alumni Achievement Award, Philadelphia, PA
- 2000 The Brock Lectureship, National Heart and Lung Institute, Imperial College, London, UK
- 2000 Anna Borun Foundation Visiting Professorship, UCLA School of Medicine, Los Angeles, CA
- 2000 Annual Visiting Professorship, Institute of Molecular Medicine, Dublin, Ireland
- 2001 Millennial Lectureship, Loyola University School of Medicine, Chicago, IL
- 2002 Hans Hecht Lectureship, University of Utah, Salt Lake City, Utah
- 2003 John Blaffer Lectureship, M.D. Anderson, Houston, Texas
- 2003 Temple University Alumni Assoc. School of Medicine Certificate of Honor, Philadelphia, PA
- 2003 2<sup>nd</sup> Annual Arthur C. Fox Visiting Professor in Cardiovascular Biology, NYU, New York, NY

#### STUDY SECTIONS/REVIEW COMMITTEES: (Selected)

- 1987-91 Member, VA Cardiovascular Merit Review Board
- 1989-92 Member, Chairman, Selection Committee for AHA Louis Katz Prize in Basic Science
- 1990-92 Member, Co-Chairman, National AHA Molecular Signaling Study Section
- 1990-92 Member, Clinical Sciences II, NIH Study Section
- 1991- 2003 Senior Scientific Advisor/Consultant, Genentech, Inc.
- 1995- Ad Hoc Reviewer, Wellcome Trust, United Kingdom
- 1996-99 Councilor, American Society for Clinical Investigation
- 1997- Member, Scientific Advisory Board (Biotechnology Investment Fund), Pictet and Cie Banquiers, Geneva, Switzerland
- 1998- Member, The Pasarow Medical Research Foundation Board and Award Committee
- 1999-2001 Advisor, Integrative Biology Program, Medical Research Council, UK
- 1999-2000 Member, Pre-Doctoral Fellowship Review Panel, (National Academy of Sciences/Howard Hughes Medical Institute)
- 2000- 2002 Member, International Advisory Panel, Wellcome Trust, UK
- 2000- Advisor, Doris Duke Charitable Foundation



Co-Chair, Innovative Clinical Research Awards (2000-2002); Chair, Clinical Interfaces Program (2002- )

- 2000-02 Scientific Advisor/Consultant, Eli Lilly, USA
- 2001- Founding Scientist, Celladon, Inc.
- 2001- 2002 Consultant, Scientific Advisory Board, Donald W. Reynolds Foundation
- 2001- Aviva Biosciences, Scientific Advisory Board, San Diego California
- 2002- International Scientific Advisory Board, The Baker Institute, Melbourne, Australia
- 2002- Scientific Advisory Board, Eumorphia, London, UK
- 2002- Advisor, Helmholtz Foundation, Germany
- 2003- Scientific Advisory Board, Autogenomics, Carlsbad, CA

#### JOURNAL REVIEWS: (Selected)

<i>Cell</i>	<i>Development</i>
<i>Molecular Cell</i>	<i>Developmental Biology</i>
<i>Developmental Cell</i>	<i>Journal of Biological Chemistry</i>
<i>Nature</i>	<i>Journal of Cell Biology</i>
<i>Nature Genetics</i>	<i>Molecular Endocrinology</i>
<i>Nature Medicine</i>	<i>New England Journal of Medicine</i>
<i>Science</i>	<i>Journal of Clinical Investigation</i>
<i>Proceedings of the National Academy of Science</i>	<i>Genomics</i>
<i>Genes and Development</i>	<i>Circulation Research</i>
<i>Molecular and Cellular Biology</i>	<i>Circulation</i>

#### EDITORIAL BOARDS: (Selected)

- 1988-91 Associate Editor, *Circulation*
- 1992-2001 Member, Editorial Board, *Circulation*
- 1991-2001 Editor-in-Chief, *Trends in Cardiovascular Medicine*
- 1992-97 Associate Editor, *Journal of Clinical Investigation*
- 1998- Board of Consulting Editors, *Journal of Clinical Investigation*
- 2001- Associate Editor, *Development (Development and Disease Section)*
- 2002- Member, Editorial Board, *Journal of Biological Chemistry*
- 2002- Senior Consultant, Editorial Board, *Journal of the American College of Cardiology*

#### UNIVERSITY DUTIES:

- 1988- Attending Physician, UCSD Medical Center
- 1989- Ph.D. Doctoral Dissertation Review Committee Member for Jason Lam, Valerie Sah, David No, Tara Rachinsky, Carlos Ibancz, John Reece, Dan Rohrer, Kirk Milhoan, Ying Lee, Kim Finley, Ed Monuki, Frank Hong, Sulip Navankassatusas, Adrienne Harris, Yimin Zou, Kim Gottshall, Terrie Ramirez, Ruth Yu, Thomas Burkholder, Frank White, John Tozer, Andrew Horvai, Elisc Lamar, Esther Ramos Merki, Gina Moore, Ming Yi-Chiang, and Harry Chiu Au.
- 1995 Member, Steering Committee, Center for Molecular Genetics
- 1995 Member, UCSD Molecular Medicine Residency Program



- 1995 Member, UCSD Science Research Park committee  
2001 Member, Search Committee for Chair of Medicine  
2001 Member, Search Committee for Joint Bioengineering Medicine Faculty Position

**SELECTED INVITED LECTURESHIPS:****2002**

- Keystone Conference on Molecular Biology of the Cardiovascular System, Keystone, Colorado  
Cold Spring Harbor Conference on Cardiovascular Biology, Cold Spring Harbor, New York  
Wellcome Trust Conference on Integrative Physiology, Keynote Lecture, London, England  
Genome Institute of the Novartis Foundation, La Jolla, California  
Zensun-Fudan University Lecture, Shanghai, China  
AHA Asian Pacific Conference on Genomics and Heart Disease, Co-Organizer/Chair/Speaker, Honolulu, Hawaii  
European Society of Cardiology Symposium on Heart Failure, Keynote Lecture, Oslo, Norway  
Novartis Foundation Symposium on Conduction System Development, London, England  
University of Oregon Health Sciences Center M.D.-Ph.D. Program, Division of Molecular Medicine, Portland, Oregon  
EMBO Meeting on Muscle Molecular Biology, Oxford, England  
UCSF, Grand Rounds, San Francisco, California  
Hans Hecht Lecture, University of Utah, Salt Lake City, Utah  
John Blaffer Lectureship, M.D. Anderson, Houston, Texas

**2003**

- AAAS Annual Meeting, Symposium Chair/Speaker, Denver, CO 2003

**SELECTED PUBLICATIONS (From a Total of over 210)**

- Arber S, Hunter JJ, Ross J Jr, Hongo M, Sansig G, Borg J, Peniard JC, Chien KR, Caroni P: MLP-deficient mice exhibit a disruption of cardiac cytoarchitectural organization, dilated cardiomyopathy, and heart failure. *Cell*. 1997 Feb 7;88(3):393-403.
- Ruiz-Lozano P, Smith SM, Perkins G, Kubalak SW, Boss GR, Sucov HM, Evans RM, Chien KR: Energy deprivation and a deficiency in downstream metabolic target genes during the onset of embryonic heart failure in *RXR $\alpha$*   $\alpha$ -/- embryos. *Development*. 1998 Feb;125(3):533-44.
- Wang Y, Huang S, Sah VP, Ross J Jr, Brown JH, Han J, Chien KR: Cardiac muscle cell hypertrophy and apoptosis induced by distinct members of the p38 mitogen-activated protein kinase family. *J Biol Chem*. 1998 Jan 23;273(4):2161-8.
- Chen J, Kubalak SW, Minamisawa S, Price RL, Becker KD, Hickey R, Ross J Jr, Chien KR: Selective requirement of myosin light chain 2v in embryonic heart function. *J Biol Chem*. 1998 Jan 9;273(2):1252-56.



Wang Y, Su B, Sah VP, Brown JH, Han J, Chien KR: Cardiac hypertrophy induced by mitogen-activated kinase kinase 7, a specific activator for c-Jun NH<sub>2</sub>-terminal kinase in ventricular muscle cells. *J Biol Chem*. 1998 Mar 6;273(13):5423-26.

Hoshijima M, Sah VP, Wang Y, Chien KR, and Brown JH: The low molecular weight GTPase RhoA regulates myofibril formation and organization in neonatal rat ventricular myocytes. Involvement of Rho kinase. *J Biol Chem*. 1998 Mar 27;273(13):7725-30.

Rockman HA, Chien KR, Choi DJ, Iaccarino G, Hunter JJ, Ross J Jr, Lefkowitz RJ, Koch WJ: Expression of a  $\beta$ -adrenergic receptor kinase 1 inhibitor prevents the development of myocardial failure in gene-targeted mice. *Proc Natl Acad Sci USA*. 1998 Jun 9;95(12):7000-05.

Chen J, Kubalak SW, Chien KR: Ventricular muscle-restricted targeting of the RXR $\alpha$  gene reveals a non-cell autonomous requirement in cardiac chamber morphogenesis. *Development*. 1998 May;125(10):1943-9.

Cao L, Zhang L, Ruiz-Lozano P, Yang Q, Chien KR, Graham RM, Zhou M: A novel putative protein-tyrosine phosphatase contains a BRO1-like domain and suppresses Ha-ras-mediated transformation. *J Biol Chem*. 1998 Aug 14;273(33):21077-83.

Adams JW, Sakata Y, Davis MG, Sah VP, Wang Y, Lewis W, Liggett SB, Chien KR, Brown JH, Dorn GW 2nd: Enhanced G $\alpha_q$  signaling: a common pathway mediates cardiac hypertrophy and apoptotic heart failure. *Proc Natl Acad Sci USA*. 1998 Aug 18;95(17):10140-5.

Gruber PJ, Kubalak SW, Chien KR: Downregulation of atrial markers during cardiac chamber morphogenesis is irreversible in murine embryos. *Development*. 1998 Nov;125(22):4427-38.

Liu X, Hwang H, Cao L, Buchland M, Cunningham A, Chen J, Chien KR, Graham R, Zhou M: Domain-specific gene disruption reveals critical regulation of neuregulin signaling by its cytoplasmic tail. *Proc Natl Acad Sci USA*. 1998 Oct 27;95(22):13024-29.

Minamisawa S, Gu Y, Ross J Jr, Chien KR, Chen J: A post-transcriptional compensatory pathway in heterozygous ventricular myosin light chain 2-deficient mice results in lack of gene dosage effect during normal cardiac growth or hypertrophy. *J Biol Chem*. 1999 Apr 9;274(15):10066-70.

Marszałek J, Ruiz-Lozano P, Roberts E, Chien KR, Goldstein L: Situs inversus and embryonic ciliary morphogenesis defects in mouse mutants lacking the KIF3A subunit of kinesin-II. *Proc Natl Acad Sci USA*. 1999 Apr 27;96(9):5043-48.

Hirota H, Chen J, Betz UA, Rajewsky K, Gu Y, Ross J Jr, Mueller W, Chien KR: Loss of a gp130 cardiac muscle cell survival pathway is a critical event in the onset of heart failure during biomechanical stress. *Cell*. 1999 Apr 16;97(2):189-98.

Chen J, Chien KR: Complexity in simplicity: monogenic disorders and complex cardiomyopathies. *J Clin Invest*. 1999 Jun;103(11):1483-5.

Sah VP, Minamisawa S, Tam SP, Wu TH, Dorn GW 2nd, Ross J Jr, Chien KR, Heller Brown J: Cardiac-specific overexpression of RhoA results in sinus and atrioventricular nodal dysfunction and contractile failure. *J Clin Invest*. 1999 Jun;103(12):1627-34.

Nakamura T, Ruiz-Lozano P, Lindner V, Yabe D, Taniwaki M, Furukawa Y, Kobuke K, Tashiro K, Lu Z, Andon N, Schaub R, Matsumori A, Sasayama S, Chien KR, Honjo T: DANCE, a novel secreted RGD protein expressed in developing, atherosclerotic, and balloon-injured arteries. *J Biol Chem*. 1999 Aug 6;274(32):22476-83.

Kuo HC, Chen J, Ruiz-Lozano P, Zou Y, Nemer M, Chien KR: Control of segmental expression of the cardiac-restricted ankyrin repeat protein gene by distinct regulatory pathways in murine cardiogenesis. *Development*. 1999 Sep 17;126(19):4223-34.



Hunter JJ, Chien KR: Signaling Pathways for Cardiac Hypertrophy and Failure. *N Engl J Med*. 1999 Oct 21;341(17):1276-83.

Knowlton KU, Chien KR: Inflammatory pathways and cardiac repair: the affliction of infarction. *Nat Med*. 1999 Oct;5(10):1122-23.

Barak Y, Nelson MC, Ong ES, Jones YZ, Ruiz-Lozano P, Chien KR, Koder A, Evans R: PPAR $\gamma$  is required for placental, cardiac, and adipose tissue development. *Mol Cell*. 1999 Oct;4(4):585-95.

Minamisawa S, Hoshijima M, Chu G, Ward C, Frank K, Gu Y, Martone M, Wang Y, Ross J Jr, Kramas EG, Giles WR, Chien KR: Chronic phospholamban-sarcoplasmic reticulum calcium ATPase interaction is the critical calcium cycling defect in dilated cardiomyopathy. *Cell*. 1999 Oct 29;99(3):313-22.

Hertig CM, Kubalak SW, Wang Y, Chien KR: Synergistic roles of neuregulin-1 and insulin-like growth factor-I in activation of the phosphatidylinositol 3-kinase pathway and cardiac chamber morphogenesis. *J Biol Chem*. 1999 Dec 24;274(52):37362-9.

Christensen G, Minamisawa S, Gruber P, Wang Y, Chien KR: High efficiency, long-term cardiac expression of foreign genes in living mouse embryos and neonates. *Circulation*. 2000 Jan 18;101(2):178-84.

Wan YJ, An D, Cai Y, Repa JJ, Chien HP, Flores M, Postic K, Magnuson MA, Chen J, Chien KR, French S, Mangelsdorf DJ, Sucov HM: Hepatocyte-specific mutation establishes RXR $\alpha$  as a heterodimeric integrator of multiple physiological processes in the liver. *Mol Cell Biol*. 2000 Jun;20(12):4436-44.

Nguyễn-Trần VTB, Kubalak SW, Minamisawa S, Fiset C, Wollert KC, Brown AB, Ruiz-Lozano P, Barrere-Lamaire S, Kondo R, Norman JW, Gourdie RG, Rahme MM, Feld GK, Clark RB, Giles WR, Chien KR: A novel genetic pathway for cardiac sudden death via defects in the transition between ventricular and conduction system cell lineages. *Cell*. 2000 Sep 1;102(5):671-82.

Chien KR: Genomic Circuits and the Integrative Biology of complex Cardiac Diseases. *Nature*. 2000 Sep 14;407(6801):227-32.

Pashmforoush M, Poumès P, Peterson KL, Kubalak SW, Ross J Jr, Hefti A, Aebi U, Beckerle MC, Chien KR: Adult mice deficient in actinin-associated LIM-domain protein reveal a developmental pathway for right ventricular cardiomyopathy. *Nat Med*. 2001 May;7(5):591-7.

Giordano FJ, Gerber HP, Williams SP, van Bruggen N, Bunting S, Ruiz-Lozano P, Gu Y, Nath AK, Huang Y, Hickey R, Dalton N, Peterson KL, Ross J Jr, Chien KR, Ferrara N: A cardiac myocyte vascular endothelial growth factor paracrine pathway is required to maintain cardiac function. *Proc Natl Acad Sci USA*. 2001 May 8;98(10):5780-5.

Wettschurck N, Rutten H, Zywiets A, Gehring D, Wilkie TM, Chen J, Chien KR, Offermanns S: Absence of pressure overload induced myocardial hypertrophy after conditional inactivation of Galphaq/Galphi1 in cardiomyocytes. *Nat Med*. 2001 Nov;7(11):1236-40.

Yasukawa H, Hoshijima M, Gu Y, Nakamura T, Pradervand S, Hanada T, Hanakawa Y, Yoshimura A, Ross J Jr, Chien KR: Suppressor of cytokine signaling-3 is a biomechanical stress-inducible gene that suppresses gp130-mediated cardiac myocyte hypertrophy and survival pathways. *J Clin Invest*. 2001 Nov;108(10):1459-67.

Kuo HC, Cheng CF, Clark RB, Lin JJC, Lin JLC, Hoshijima M, Nguyễn-Trần VTB, Gu Y, Ikeda Y, Chu FH, Ross J Jr, Giles WR, Chien KR: A defect in the Kv Channel-Interacting Protein 2 (KChIP2) gene leads to a complete loss of I<sub>to</sub> and confers genetic susceptibility to ventricular tachycardia. *Cell* 107: 801-813, 2001.

Nakamura T, Ruiz-Lozano P, Ikeda Y, Iwanaga Y, Hinek A, Minamisawa S, Cheng CF, Kobuke K, Dalton N, Takada Y, Tashiro K, Ross J Jr, Honjo T, Chien KR: Fibulin-5/DANCE is essential for elastogenesis in vivo. *Nature*. 415:171-5.



2002.

Crone S, Zhao YY, Fan L, Gu Y, Minamisawa S, Peterson KL, Chen J, Kahn R, Condorelli G, Ross J Jr, Chien KR, Lee KF: ErbB2 is Essential in the Prevention of Dilated Cardiomyopathy. *Nat Med.* 8:459-465, May 2002.

Ozcelik C, Erdmann B, Pilz B, Wettchurack N, Britsch S, Hubner N, Chien KR, Birchmeier C, Garratt A: Conditional mutation of the ErbB2 (HER2) receptor in cardiomyocytes leads to dilated cardiomyopathy. *Proc Natl Acad Sci USA.* Vol 99:13, 8880-8885, June 2002

Hoshijima M, and Chien KR: Mixed Signals in Heart Failure: Cancer Rules, *JCI*, 109:849-855, 2002.

Hoshijima M, Ikeda Y, Ross J Jr, Chien KR: Chronic Inhibition of Heart Failure by a Pseudophosphorylated Mutant of Phospholamban via an In Vivo Cardiotropic rAAV Gene Delivery System. *Nature Medicine*, 8: 864-871, August 2002.

Chien KR, Olson EN: Converging Pathways and Principles in Heart Development and Disease. *Cell.* 110(2):153-62, July 2002.

Zhao YY, Liu Y, Stan RV, Fan L, Gu Y, Dalton N, Chu PH, Peterson K, Ross J Jr, Chien KR: Defects in caveolin-1 cause dilated cardiomyopathy and pulmonary hypertension in knockout mice. *PNAS* 2002 99: 11375-11380.

Knöll R, Hoshijima M, Bang M, Yasukawa H, Person V, Lorenzen-Schmidt I, Scott C, Hayashi T, Kimura A, Shiga N, Yokoyama M, Omens J, McKenna W, McCulloch A, Gregorio C, Fuller W, Schaper W, Schaper J, Schultheiss HP, Chien KR: The Cardiac Mechanical Stretch Sensor Machinery involves a Z Disc Complex that is Defective in a Subset of Human Dilated Cardiomyopathy. *Cell*, Vol. 111, 943-955, December 27, 2002

Hamblet NS, Lijam N, Ruiz-Lozano R, Wang J, Yang Y, Luo Z, Mei L, Chien KR, Sussman DJ, Wynshaw-Boris A: Dishevelled 2 is essential for cardiac outflow tract development, somite segmentation and neural tube closure. *Development*. 2002 129: 5827-5838

Ludwig A, Budde T, Stieber J, Moosmang S, Wahl C, Holthoff K, Langebartels A, Wotjak C, Munsch T, Zong X, Feil S, Feil R, Lancel M, Chien KR, Konnerth A, Pape H, Biel M, Hoffman F: Absence epilepsy and sinus dysrhythmia in mice lacking the pacemaker channel HCN2. *EMBO J*, Jan 15;22 (2):216-24, 2003.

Ruiz-Lozano, P, and Chien, K.R.: Cre-constructing the Heart, *Nature Genetics*, Vol 33, pp8-9, January 2003

Chien, K.R.: Genotype, Phenotype: Upstairs, Downstairs in the Family of Cardiomyopathies, *JCI*, 111:175-178, 2003

Cheng, C.F, Kuo, H.C, and Chien, K.R.: Genetic Modifiers of Cardiac Arrhythmias, *Trends in Molecular Medicine*, Vol 9:2, 59-66, 2003

Hoshijima, M, Knoll, R, and Chien, K.R.: Stress Pathways and Heart Failure: The MLP Story, *Cold Spring Harbor Quantitative Symposium Proceedings*, In Press, 2003

#### **Books:**

*Molecular Basis of Cardiovascular Disease*, Editor, K. R. Chien; Section Editors, J. Breslow, J. Leiden, R. Rosenberg, C. E. Seidman, W. B. Saunders Co., Cambridge, MA. (Companion text to E. Braunwald's *Heart Disease*), 1999.

*Molecular Basis of Cardiovascular Disease, Second Edition*, Editor, K.R. Chien; Elsevier Science Publishing Co., 2003, In Press.